1. NAME OF THE MEDICINAL PRODUCT

Crinone 80 mg/g vaginal gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g vaginal gel contains 80 mg of progesterone.

Each applicator delivers 1.125 g of vaginal gel containing 90 mg of progesterone.

Excipient with known effect:

Sorbic acid 0.9 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal gel
A smooth white to off-white gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Progesterone supplementation of the luteal phase in adults as part of an ART (assisted reproductive technology) procedure.

4.2 Posology and method of administration

Posology

From the day of embryo transfer, 1.125 g Crinone vaginal gel (90 mg progesterone) should be inserted into the vagina once daily. Once the laboratory findings confirm pregnancy, this therapy should be continued for a total treatment duration of 30 days.

Small white globules may appear as vaginal discharge possibly due to gel accumulation, up to several days after usage.

Paediatric population
There is no relevant use of Crinone in the paediatric population.

Method of administration

Patients should be instructed on how to administer Crinone, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Undiagnosed vaginal bleeding.
- Known or suspected malignancy of the breast or genital organs.
- Porphyria.
- Thrombophlebitis, thromboembolic disorder, cerebral apoplexy, or patients with a history of these conditions.

- Missed abortion.

4.4 Special warnings and precautions for use

Crinone includes sorbic acid as an excipient. Sorbic acid may cause local skin reactions (e.g. contact dermatitis). Local skin reactions might also occur on the penis of the partner when having intercourse following vaginal application of Crinone. This may be prevented by the use of condoms.

Gynaecological check-ups are required before and regularly under therapy with the drug; endometrial hyperplasia in particular should be ruled out as part of these controls under longer-term treatment. The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.

If during therapy with Crinone, threatened abortion occurs, embryo viability should be established using rising HCG titers and/or ultrasound.

Careful use in the event of severe liver impairment.

In cases of breakthrough bleeding, as in all cases of irregular vaginal bleeding, non-functional causes should be considered. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures should be undertaken.

Because progestogens may cause some degree of fluid retention, conditions that might be influenced by this factor (e.g. epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.

The pathologist should be advised of progesterone therapy when relevant specimens are submitted.

Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

A decrease in glucose tolerance has been observed in a small number of patients on oestrogen-progestin combination drugs. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.

The physician should be alert to the early manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorder, pulmonary embolism and retinal thrombosis). Should any of these thrombotic disorders occur or be suspected, the drug should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

4.5 Interactions with other medicinal products and other forms of interaction

The drug should not be administered simultaneously with other intravaginal therapies.

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Crinone is not indicated during pregnancy except for use in early pregnancy as part of an ART regimen (see section 4.2). A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no association between the maternal use of natural progesterone in early pregnancy and foetal malformations.

Breastfeeding
The use of Crinone is not recommended during lactation.

Fertility
Crinone is indicated for the use of progesterone supplementation of the luteal phase in adults as part of an ART (assisted reproductive technology) procedure (see section 4.1).

4.7 Effects on ability to drive and use machines

Fatigue can arise during the use of Crinone.
Caution is required when driving and operating machinery during pregnancy.
It should be remembered in particular that alcohol could further worsen the ability to drive.

4.8 Undesirable effects

The following definitions apply to the frequency terminology used hereafter:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Frequency not known (cannot be estimated from the available data)

Immune system disorders
Frequency not known: hypersensitivity reactions usually manifesting as skin rash e.g. generalized itchy skin rash, vulvovaginal swelling, swelling of the breasts and face.

Psychiatric disorders
Common: somnolence.

Gastrointestinal disorders
Common: abdominal pain/ cramps.

Reproductive system and breast disorders
Common: breast tenderness, intermenstrual bleeding (spotting).

General disorders and administration site conditions
Common: headache, vaginal irritation and other mild application site reactions.

During post-marketing surveillance, clumping/coagulation/accumulation of Crinone gel has been reported. These events are usually non-serious and appear with beige to brownish clumpy or sometimes cloudy white discharge. The gel clumping/coagulation/accumulation can be associated with vaginal irritation, pain and swelling; very rarely, it might also cause cramps and vaginal bleeding.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Overdosage is not anticipated as each dose is applied through an individual disposable applicator. However, if it occurs, treatment with Crinone should be discontinued.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, Progestogens,
ATC code: G03DA04

The properties are the same as those of naturally occurring progesterone with induction of the secretory phase in the endometrium.

5.2 Pharmacokinetic properties

Crinone represents a delayed-release system, based on the carbomer-polycarbophil polymer combination, which results in adhesion of the gel to the vaginal mucosa. In this way, continuous release of the active substance progesterone is achieved over a period of 72 hours maximum and absorption is prolonged.

Relative bioavailability of Crinone is approximately 20% compared to intramuscular progesterone.

Absorption
After a single dose of Crinone, peak plasma levels of approximately 11-15 ng/ml were measured after about 7 hours.

Upon repeated once daily administration of Crinone, steady-state was achieved within the first 24 hours of treatment; mean steady-state concentrations were approximately 9 ng/ml.

Metabolism
Progesterone is mainly metabolised in the liver (by reduction, hydroxylation and conjugation) with subsequent glucuronidation of the metabolites.

The main metabolite is 3α, 5β-pregnanediol (pregnanediol).

However, it is of note that due to the vaginal application of progesterone, the hepatic first-pass effect is avoided.

Elimination
Excretion mainly takes place via the urine in the form of the pregnanediol metabolite. The elimination half-life is between 34 and 48 hours.

Special populations
There are no pharmacokinetic data available in specific patient groups (children / adolescents, elderly, hepatic and renal impairment).

5.3 Preclinical safety data

Due to the pronounced differences among the test animals, as well as related to humans, animal studies with progesterone possess only a limited predictive value for use in humans.

Crinone demonstrated acceptable vaginal tolerability in rabbits with higher rates of application and greater volumes than intended for therapeutic use. No evidence of a dermal sensitising potential was found in guinea-pigs using Crinone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbic acid (E 200),
glycerol, liquid paraffin,
hydrogenated palm oil glycerides,
carbomer 974P,
polycarbophil,
sodium hydroxide,
purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.
Do not freeze.

6.5 Nature and contents of container

The vaginal gel is filled in single-use, one piece, white polyethylene vaginal applicators with a twist-off top, each sealed in a paper/aluminium/ionomer resin foil overwrap.

Each applicator contains 1.45 g of vaginal gel but delivers a controlled 1.125 g of vaginal gel.
The product is supplied in packs of 6 or 15 single-dose applicators.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The application of Crinone with the applicator should preferably ensue in the mornings and in a lying position with slightly bent knees.

Remove the applicator from the packaging without opening it immediately.

Hold the applicator firmly at the end for a few seconds so that the contents collect at the opening of the applicator.

Open the applicator, place it deep into the vagina while in a lying position and firmly press the end of the applicator.

Each applicator is intended for single use only. Any content of vaginal gel remaining in the applicator after use must be discarded and disposed of in accordance with local requirements.